Erythromycin and Common Cold in COPD*

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Study objectives: To investigate whether erythromycin therapy lowers the frequency of the common cold and subsequent exacerbation in patients with COPD.

Design: Prospective, randomized, controlled, but not blinded, trial.

Patients: One hundred nine patients with COPD were enrolled into the study. Patients were randomly assigned to erythromycin therapy or to no active treatment in September 1997. Patients then were observed for 12 months, starting in October, during which time the risk and frequency of catching common colds and COPD exacerbations were investigated. Fifty-five patients received erythromycin at study entry (erythromycin group). The remaining 54 patients received no active treatment (control group).

Measurements and results: The mean (± SE) number of common colds for 12 months was significantly lower in the erythromycin group than in the control group (1.24 ± 0.07 vs 4.54 ± 0.02, respectively, per person; p = 0.0002). Forty-one patients (76%) in the control group experienced common colds more than once, compared to 7 patients (13%) in the erythromycin group. The relative risk of developing two or more common colds in the control group compared with that in the erythromycin group was 9.26 (95% confidence interval [CI], 3.92 to 31.74; p = 0.0001). Thirty patients (56%) in the control group and 6 patients (11%) in the erythromycin group had one or more exacerbations. The relative risk of experiencing an exacerbation in the control group compared with that in the erythromycin group was 4.71 (95% CI, 1.53 to 14.5; p = 0.007). Significantly more patients were hospitalized due to exacerbations in the control group than in the erythromycin group (p = 0.0007).

Conclusion: Erythromycin therapy has beneficial effects on the prevention of exacerbations in COPD patients.

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Key words: common cold; COPD; erythromycin; exacerbation; lower airway infection

Abbreviations: HRV = human rhinovirus; ICAM = intercellular adhesion molecule

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ommon colds often predispose patients with COPD to develop lower airway infections,1 which are one of the most common causes of exacerbations in COPD patients. Several viral infections, such as human rhinoviruses (HRVs),2 respiratory syncytial viruses, or influenza and para-influenza viruses, are related to exacerbations of COPD.3,4 An epidemiologic study revealed that patients with COPD experienced more acute lower respiratory infections than did healthy subjects, and that total respiratory illness rates were higher as well.5

Low-dose and long-term erythromycin therapy has been reported6 to be effective in treating patients with diffuse panbronchiolitis or bronchiectasis via mechanisms other than antibacterial activity. Likewise, azithromycin is effective in preventing Pneumocystis carinii pneumonia in HIV-1-infected patients.7 However, to our knowledge, the efficacy of erythromycin therapy for the prevention of the common cold and subsequent exacerbations in COPD patients has not been reported on. We therefore investigated whether erythromycin therapy lowers the frequency of common colds and exacerbations of COPD in a prospective, randomized, controlled trial.

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MATERIALS AND METHODS

We prospectively compared the rate and number of common colds and exacerbations in COPD patients treated with erythromycin with those in COPD patients who did not receive erythromycin therapy. All patients fulfilled the criteria for COPD of the American Thoracic Society. We excluded patients with bronchiectasis or diffuse panbronchiolitis from the study. COPD patients participating in this study were treated with sustained-release theophylline and inhaled anticholinergic agents but did not receive corticosteroids.

Randomization was performed by a random-number table, and the list was held independently of the investigators. This study was not blinded. One hundred nine patients, from whom written informed consent had been obtained, were randomly assigned to receive erythromycin (200 to 400 mg/d) therapy or no active treatment (riboflavin, 10 mg/d) in September 1997. Fifty-five patients received erythromycin at study entry (erythromycin group). Patients enrolled into the erythromycin group were treated with erythromycin until the end of the study, unless they experienced apparent adverse effects as a result of receiving it. The remaining 54 patients received riboflavin (control group). The study was approved by the Tohoku University Ethics Committee.

Patients then were observed for 12 months, starting in October, 4 weeks after erythromycin or riboflavin was given, during which time the following 10 symptoms were recorded: sneezing; nasal discharge; nasal congestion; malaise; headache; chills; feverishness; sore throat; hoarseness; and cough. Symptoms were rated for severity on a scale from 0 to 3 and were recorded on daily record cards. A common cold was defined as a total symptom score of > 5. Patients visited the hospital every 2 weeks, and their physical condition was evaluated by their doctors. It was also recommended that they visit the hospital for investigator-initiated checks if their total symptom score was > 5.

We defined a COPD exacerbation as an acute and sustained worsening of COPD symptoms requiring changes to regular treatment, including antimicrobial therapy and/or short courses of systemic steroids. We classified the severity of the exacerbation as mild to moderate if patients could be treated without hospitalization, and as severe if hospitalization were required.

Data are presented as the mean ± SE. The Cox proportional hazards model was used to compare the relative risk of developing a common cold and the relative risk of an exacerbation of COPD between the control and erythromycin group. In other analyses, the unpaired t test was used to compare parameters between the two groups. Significance was accepted at p < 0.05.

RESULTS

None of the patients in either group died during the study period. In the erythromycin group, one patient experienced anorexia and diarrhea during the observation period and was excluded from the study. The rest of the patients in the erythromycin group did not have any apparent adverse effects from erythromycin therapy during the study period.

The two groups did not differ in age, sex, vital capacity, FEV1, PaO2, or PaCO2 (Table 1). The number of common colds for 12 months was significantly lower in the erythromycin group (1.24 ± 0.07 per person) than in the control group (4.54 ± 0.02 per person; p = 0.0002) [Table 2].

During the study period, 41 of 54 patients (76%) in the control group experienced common colds more than once, compared to 7 of 54 patients (13%) in the erythromycin group. The relative risk of developing common colds more than once a year in the control group was 9.26 (95% confidence interval, 3.92 to 31.74; p = 0.0001).

The total number of exacerbations was significantly lower in the erythromycin group compared to that in the control group (p < 0.0001) (Table 2). Sixty-four COPD exacerbations (26%) related to 245 common colds occurred in the control group, and 14 exacerbations related to 67 common colds (21%) occurred in the erythromycin group. Thirty patients (56%) in the control group and 6 patients (11%) in the erythromycin group had at least one exacerbation. The relative risk of experiencing one or more exacerbations in the control group compared with that in the erythromycin group was 4.71 (95% confidence interval, 1.53 to 14.5; p = 0.007).

Data are presented as the mean ± SE. The Cox proportional hazards model was used to compare the relative risk of developing a common cold and the relative risk of an exacerbation of COPD between the control and erythromycin group. In other analyses, the unpaired t test was used to compare parameters between the two groups. Significance was accepted at p < 0.05.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control Group (n = 54)</th>
<th>Erythromycin Group (n = 55)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>71.7 (0.89)</td>
<td>69.1 (1.67)</td>
<td>0.1420</td>
</tr>
<tr>
<td>Sex, No.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>44</td>
<td>47</td>
<td>0.8226</td>
</tr>
<tr>
<td>Female</td>
<td>10</td>
<td>7</td>
<td></td>
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<tr>
<td>Height, cm</td>
<td>159.3 (0.92)</td>
<td>158.6 (1.21)</td>
<td>0.6623</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>52.5 (1.00)</td>
<td>55.0 (1.39)</td>
<td>0.1369</td>
</tr>
<tr>
<td>Vital capacity, L</td>
<td>2.61 (0.08)</td>
<td>2.67 (0.16)</td>
<td>0.6025</td>
</tr>
<tr>
<td>FEV1, L/s</td>
<td>1.30 (0.08)</td>
<td>1.47 (0.15)</td>
<td>0.2601</td>
</tr>
<tr>
<td>PaO2, mm Hg</td>
<td>73.8 (1.43)</td>
<td>74.6 (1.90)</td>
<td>0.7501</td>
</tr>
<tr>
<td>PaCO2, mm Hg</td>
<td>42.4 (0.68)</td>
<td>43.5 (1.21)</td>
<td>0.4212</td>
</tr>
</tbody>
</table>

*Values given as mean (SE), unless otherwise indicated.

<table>
<thead>
<tr>
<th>Measures</th>
<th>Control Group (n = 54)</th>
<th>Erythromycin Group (n = 55)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total common colds, No.</td>
<td>245</td>
<td>67</td>
<td>0.0002</td>
</tr>
<tr>
<td>Total patients with two or more common colds, No.</td>
<td>41</td>
<td>7</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Total number of exacerbations, No.</td>
<td>64</td>
<td>14</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Mild/moderate</td>
<td>53</td>
<td>14</td>
<td>0.0087</td>
</tr>
<tr>
<td>Severe</td>
<td>11</td>
<td>0</td>
<td>0.0007</td>
</tr>
<tr>
<td>Total patients with one or more exacerbations, No.</td>
<td>30</td>
<td>67</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Mild/moderate</td>
<td>20</td>
<td>6</td>
<td>0.0004</td>
</tr>
<tr>
<td>Severe</td>
<td>10</td>
<td>0</td>
<td>0.0004</td>
</tr>
</tbody>
</table>
Acute respiratory infections long have been viewed by clinicians as a particular problem for patients with COPD. Bacterial airway infections frequently followed by common colds produce exacerbations and sometimes life-threatening conditions in COPD patients. HRVs, the most common cause of the common cold, can cause exacerbations of asthma or COPD, presumably via the immune response to the infection. These exacerbations highlight the need for more effective means of preventing common colds in COPD patients.

Up to now, several attempts have been made to prevent the catching of colds or to cure colds. Vitamin C supplementation and the common cold has long been controversial since Linus Pauling claimed that vitamin C prevents and alleviates the episode of the common cold. Zinc gluconate lozenges were expected to reduce the symptoms and duration of the common cold, but a randomized, controlled trial revealed that they were not effective. Corticosteroid therapy with either oral prednisone or intranasal fluticasone propionate does not have any marked effect on the symptoms of the common cold, but rather induces higher viral titers or prolonged shedding of viable virus. Several attempts to target HRVs were made. WIN 52084, an antiviral agent that inhibits viral structural dynamics, was not effective at all in reducing cold symptoms, while it inhibited rhinovirus infection in vitro. Soluble intercellular adhesion molecule (ICAM)-1, which binds to the HRV receptor and inhibits the virus from adhering to the airway epithelium, reduced the severity of experimental rhinovirus colds in humans. So far, soluble ICAM-1 is the only possible agent that may be useful in alleviating the symptoms of the common cold.

In this study, we showed that low-dose, long-term erythromycin treatment significantly reduced the rate of catching colds in patients with COPD. The same therapy has been reported to dramatically improve the prognosis for patients with diffuse panbronchiolitis or other chronic lower respiratory tract infections. Also, erythromycin dose dependently improved the survival rate and inhibited inflammatory cell responses in murine influenza virus-induced pneumonia models. These beneficial effects of erythromycin are considered to be due to an anti-inflammatory mechanism rather than to an anti-infective mechanism. Erythromycin suppresses the expression and release of interleukin-6, interleukin-8, and ICAM-1 in human bronchial epithelial cells. It is therefore possible that erythromycin may reduce the symptoms of colds by suppressing inflammatory cytokines in COPD patients.

On the other hand, macrolide antibiotics have been reported to have effects other than anti-inflammatory or antibacterial. For example, azithromycin is effective in preventing P. carinii pneumonia in HIV-1-infected patients. It has been reported that bafilomycin A1, a kind of macrolide antibiotic as well as a specific vacuolar H+-ATPase inhibitor, inhibited both major and minor HRV infections in HeLa cells by preventing viruses from entering the cytoplasm. Therefore, erythromycin may prevent COPD patients from catching common colds by inhibiting HRV infection, which is the most common cause of colds in adults. Likewise, patients with moderate-to-severe COPD are reported to be more susceptible to infection with Mycoplasma pneumoniae than are healthy adults or patients with mild COPD. Erythromycin has anti-infection effects for this pathogen and may prevent COPD patients from Mycoplasma infection.

The increasing emergence of macrolide-resistant respiratory pathogens, both Haemophilus influenzae and, more often, Streptococcus pneumoniae, has become a growing concern. In this study, we treated the 54 COPD patients with prolonged low-dose erythromycin. As a consequence, there will arise a potential serious risk that could result from the widespread emergence of resistant strains in COPD patients who already are at a particularly high risk for developing respiratory infections due to these pathogens. In this study, the frequency of the COPD exacerbations and hospitalization due to the exacerbations were lowered in the control group to 22 to 0%, respectively, when erythromycin was used in COPD patients. This beneficial significance of lowering the frequency of an exacerbation and its severity may overwhelm the serious theoretical risk that could be associated with the intervention being studied if erythromycin therapy is used solely in patients with moderate-to-severe COPD on whom exacerbations may have a significant impact on their functional capacities and their lives in general.

In conclusion, our findings suggest that not only the frequency and risk of exacerbations, but also their severity, can be lowered if sustained low-dose erythromycin therapy is used in COPD patients. However, this intervention should be restricted to patients who are at high risk for exacerbations of COPD because of the potential risk for the emergence of erythromycin-resistant pathogens.
REFERENCES